Investigation of tryptophan hydroxylase 2 (TPH2) in schizophrenia and in the response to antipsychotics

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Abstract: Serotonergic transmission is considered relevant in the pathophysiology and the treatment of schizophrenia. Tryptophan hydroxylase (TPH) is the rate limiting enzyme in the biosynthesis of serotonin. While the TPH1 gene has been found to be associated with schizophrenia, studies focusing on TPH2 variants did not yield conclusive results for schizophrenia or the response to antipsychotic medication. We analyzed eleven TPH2 SNPs in two case-control samples consisting of 4453 individuals in total. Six SNPs were selected because of their potential functional relevance (rs4570625, rs11178997, rs11178998, rs7954758, rs7305115, and, rs4290270) and were supported by another 5 tagging SNPs selected based on HapMap LD information. In the discovery sample (1476 individuals), we observed a significant association with schizophrenia for rs10784941 (p = 0.009, OR minor G-allele 0.82 [0.71-0.95]) and rs4565946 (p = 0.011, OR minor T-allele 0.83 [0.71-0.96]). Association was also observed with a common rs4570625-rs4565946 haplotype (OR G-C haplotype 1.20 [1.02-1.40]; p = 0.0046). Single-marker associations could not be replicated in the replication sample consisting of 2977 individuals, but there was a strong trend regarding the rs4570625-rs4565946 G-C haplotype (OR 1.10 [0.98-1.24]; p(one-sided test) = 0.054). In smaller sub-samples, the rare rs4570625-rs4565946 T-T haplotype was associated with reduced processing speed (n = 193, p = 0.004) and sensorimotor gating (n = 68, p = 0.006) of schizophrenia patients. TPH2 variants and the rs4570625-rs4565946 G-C haplotype did not influence the beneficial response to antipsychotic drugs (n = 210) after four weeks of treatment administering the Positive and Negative Syndrome Scale of Schizophrenia (PANSS). We also investigated the association of the SNPs to treatment response, but did not get significant results. In sum, our results argue for only a minor role of TPH2 in schizophrenia.

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Investigation of Tryptophan hydroxylase 2 (TPH2) in schizophrenia and in the response to antipsychotics

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ABSTRACT

Serotonergic transmission is considered relevant in the pathophysiology and the treatment of schizophrenia. Tryptophan hydroxylase (TPH) is the rate limiting enzyme in the biosynthesis of serotonin. While the TPH1 gene has been found to be associated with schizophrenia, studies focussing on TPH2 variants did not yield conclusive results for schizophrenia or the response to antipsychotic medication. We analyzed eleven TPH2 SNPs in two case-control samples consisting of 4,453 individuals in total. Six SNPs were selected because of their potential functional relevance (rs4570625, rs11178997, rs11178998, rs7954758, rs7305115, and, rs4290270) and were supported by another 5 tagging SNPs selected based on HapMap LD information. In the discovery sample (1,476 individuals), we observed a significant association with schizophrenia for rs10784941 (p=0.009, OR minor G-allele 0.82 [0.71-0.95]) and rs4565946 (p=0.011, OR minor T-allele 0.83 [0.71-0.96]). Association was also observed with a common rs4570625-rs4565946 haplotype (OR G-C haplotype 1.20 [1.02-1.40]; p=0.0046). Single-marker associations could not be replicated in the replication sample consisting of 2,977 individuals, but there was a strong trend regarding the rs4570625-rs4565946 G-C haplotype (OR 1.10 [0.98-1.24]; p(one-sided test)=0.054). In smaller subsamples, the rare rs4570625-rs4565946 T-T haplotype was associated with reduced processing speed (n=193, p=.004) and sensorimotor gating (n=68, p=.006) of schizophrenia patients. TPH2 variants and the rs4570625-rs4565946 G-C haplotype did not influence the beneficial response to antipsychotic drugs (n=210) after four weeks of treatment administering the Positive and Negative Syndrome Scale of Schizophrenia (PANSS). We also investigated the association of the SNPs to treatment response, but did not get significant results. In sum, our results argue for only a minor role of TPH2 in schizophrenia.

Keywords: TPH2, schizophrenia, association study, response antipsychotics, cognition, PPI

1. Introduction

Serotonergic transmission is considered relevant in the pathophysiology (Abi-Dargham et al., 1997; Kishi et al., 2009) and the treatment of schizophrenia. Especially the serotonin receptor genes HTR1A and HTR2A play an important role in the pharmacogenetic response to antipsychotic treatment (Arranz et al., 1996; Arranz & de Leon, 2007; Mössner et al., 2009; Reynolds et al., 2006; Wang et al., 2008). Although many 5-HT receptor subtypes mediate the serotonergic transmission (Mössner et al., 2006a), the availability of serotonin also depends on its biosynthesis which is initiated by tryptophan hydroxylase (TPH). Serotonin is produced by generating 5-hydroxytryptophan out of tryptophan and the downstream decarboxylation using aromatic amino acid decarboxylase (Walther & Bader, 2003). Therefore TPH is the rate limiting enzyme in the biosynthesis of serotonin (Marziniak et al., 2009). Two TPH isoforms have been discovered in humans. Until recently, only one isoform (TPH1) was considered to be responsible for the 5-HT synthesis in the brain and in the periphery. In 2003, studies examining TPH knockout mice showed that serotonin levels were normal in most brain regions whereas serotonin was greatly diminished in the periphery (Walther & Bader, 2003; Walther et al., 2003). A second isoform (TPH2) was found, which has 71% amino acid identity with the isoform TPH1 (Walther & Bader, 2003). Many studies examining the expression of TPH1 and TPH2 strengthen the duality hypothesis saying that TPH1 is responsible for the periphery and TPH2 for the central nervous system respectively (Patel et al., 2004; Walther & Bader, 2003; Zill et al., 2009).

Postmortem brain analysis, cerebrospinal fluid studies, and pharmacological challenges suggest an impaired serotonin functioning in the cortex of patients with schizophrenia (Abi-Dargham et al., 1997). Furthermore 5-HT receptors might play a role in the predominant therapy response to antipsychotics (Meltzer et al., 2003). The TPH1 gene has been found to be associated with schizophrenia (Li & He, 2006; Saetre et al., 2009; Zaboli et al., 2006). The TPH1 isoform in mouse brain stem is expressed 150 times lower than TPH2 and recent studies suggest that TPH2, which is mainly expressed in the brain, is more relevant in the pathophysiology of psychiatric disorders. But until now studies investigating the association of TPH2 variants with schizophrenia or the response to antipsychotic medication in dependence from TPH2 genotypes did not yield conclusive results. De Luca et al.

(2005) compared healthy controls with schizophrenia patients and found that schizophrenic individuals only showed a trend towards increased TPH2 mRNA levels compared to controls (De Luca et al., 2005). But the authors themselves remarked that the power of this analysis was very small with 0.18. In Japanese patients as well as in Malay patients no association was found between two variants and one variant of the TPH2 gene respectively, and schizophrenia (Higashi et al., 2007; Tee et al., 2010). In another association study among Japanese patients neither one of the 15 analyzed TPH2 variants nor their haplotypes were significantly associated with schizophrenia (Shiroiwa et al., 2011). In a fourth association analysis in a Korean sample none of the six investigated TPH2 variants (rs4570625, rs10748185, rs11179027, rs1386498, rs4469933, and rs17110747) were associated with schizophrenia or with the improvement of positive or negative symptomatology measured with the PANSS (Serretti et al., 2011). Zhang et al. 2011 (2011) did also not find an association of three TPH2 variants with schizophrenia in a Chinese sample. It is noteworthy that the allelic distribution of genetic variants differs with the ethnicity of the analyzed sample.

Since four out of five association analyses were performed with Asian patients, a systematic investigation of TPH2 in Caucasian populations is clearly missing. Despite the missing evidence for association, such a study is, nevertheless, of interest due to, first, the biological plausibility for the association of TPH2 gene with the pathophysiology of schizophrenia and, secondly, the results that serotonin functioning in the cortex of patients with schizophrenia is impaired (Abi-Dargham et al., 1997). Therefore, we set out to conduct an extensive study focussing on TPH2, including association analysis between genetic variants and schizophrenia, analysis of promising endophenotypes and analysis of response to psychotic therapy. In more detail, in a pilot study with a sample consisting of 788 schizophrenia patients and 688 healthy controls, we investigated 11 SNP markers and their haplotypes. We tried to replicate our finding in an independent replication sample consisting of 943 schizophrenia patients and 2034 healthy controls. Since previous studies detected hints of association with schizophrenia endophenotypes (Zhang et al. 2011; Serretti et al., 2011), we enlarged the spectrum of our analysis to the established schizophrenia endophenotypes sensorimotor gating (Gottesman & Gould, 2003; Quednow et al., 2008a) and cognitive functioning. In order to complete the picture

and to investigate a potential link of our findings to therapy, we also investigated response on psychotropic medication. The analysis of the endophenotypes and drug response were carried out in three subsamples and focussed on a haplotype highlighted by our association study.

2. Material and methods

2.1. Participants: Association study

Schizophrenia inpatients were recruited from the Departments of Psychiatry and Psychotherapy at the Universities of Bonn, Düsseldorf, Munich, and the Central Institute of Mental Health in Mannheim. Schizophrenia was diagnosed according to the ICD-10 criteria for schizophrenia using structured interviews (DSM-IV, SKID). The healthy control subjects were identified via local city address registers and public notices and were all screened for the absence of psychiatric disorders by case history questionnaires. All patients and controls were of German Caucasian origin.

The discovery sample consisted of 788 schizophrenia patients (470 males), who had an average age of 34.2 years, and 688 controls (326 males), who had an average age of 38.9 years. All patients and controls gave written informed consent to participate in the study. The study was approved by the appropriate ethics committees. All subsamples of schizophrenia patients described below were included in this discovery sample, see also table 1 for sample characteristics.

The replication study consisted of 943 schizophrenia inpatients and 2034 healthy controls. The 943 schizophrenia patients (592 males) had an average age of 37.8 years, while the 2034 controls (995 males) had an average age of 50.8 years.

2.2. Participants and methods: Cognitive functioning and sensorimotor gating

A subset of 193 schizophrenia patients (mean age of 36.4 years, 109 males), the NP (neuropsychological response) sample, was assessed with a cognitive test battery as described in our previous study (Mössner et al., 2008). In short, five frequently used neuropsychological tests were assessed. Dependent measures and the corresponding tests were (1) the sensitivity score *d'* of the Continuous Performance Test (CPT-IP) (Cornblatt et al., 1988), (2) the number of correctly coded symbols within the digit-symbol-substitution-task (DSST) (Wechsler, 1997), (3) free delayed recall (30 min) as measured by the Rey Auditory Verbal Learning Test (RAVLT) (Helmstaedter et al., 2001), (4) time to finish part B of the Trail-Making-Test (TMT) (Reitan & Wolfson, 1993), and (5) words produced in a lexical fluency task within 1 min (letters S/A/B/N) (Benton & Hamsher, 1989). The neuropsychological

assessments were done by trained and experienced psychologist or study nurses blind for genotype. All patients who underwent neuropsychological testing were screened for the absence of neurological disturbances and mental retardation. In order to minimize psychopharmacological effects, all assessments were done when the patients were on stable medication. In a second subset (ASR / PPI sample, table 1) of 68 schizophrenia patients (mean age of 34.8 years, 46 males) exclusively recruited in the Department of Psychiatry and Psychotherapy, University of Bonn, sensorimotor gating (prepulse inhibition, PPI), startle response and habituation of the acoustic startle response (ASR) was recorded and analyzed as described in detail in our previous work (Quednow et al., 2006; Quednow et al., 2008b; Quednow et al., 2010). From the ASR / PPI sample, 14 patients were unmedicated, 12 patients received first-generation antipsychotics, and 44 were treated with second-generation antipsychotics. The treated individuals were under stable medication. There was no correlation between TPH2 haplotypes and medication type.

2.3. Participants and methods: Psychopathology during antipsychotic therapy

Pharmacogenetic analyses were performed in a further subsample of the initial case control sample. It consisted of 210 schizophrenia patients (131 male) with a mean age of 32.7 years. Thereof, 69 were enrolled in a multicentre, randomized, double-blind comparison of risperidone and haloperidol conducted at psychiatric university hospital centres in Germany within the framework of the German Research Network on Schizophrenia (Wölwer et al., 2003). Patients were randomly assigned to either risperidone or haloperidol treatment for four weeks (Gaebel et al., 2004; Möller et al., 2008). Risperidone or haloperidol was given at a dose of two milligram/day, up to a maximum of eight mg/day, if required. 32 patients were treated with haloperidol; 37 with risperidone. The only additional psychotropic drugs permitted during the study were benzodiazepines. Exclusion criteria were: pregnancy, contraindication to neuroleptic treatment, mental retardation, organic brain disease, substance abuse/dependence, and suicidal behavior in previous history (Gaebel et al., 2004). 141 schizophrenia patients were admitted to the Department of Psychiatry and Psychotherapy of the University of Bonn due to an exacerbation of psychotic symptoms and they were treated with atypical antipsychotics. The atypical

antipsychotics used included olanzapine (n=63), amisulpride (n=47), clozapine (n=18), quetiapine (n=19), risperidone (n=13), ziprasidone (n=10), aripiprazole (n=7), bifeprunox (n=3), and iloperidone (n=1). Treatment with more than one atypical antipsychotic resulted from insufficient clinical response or side-effects (n=46) while the majority of the patients were treated with only one drug (n=95). Some patients were treated with more than one atypical antipsychotic. In both studies schizophrenia was diagnosed according to the ICD-10 criteria for schizophrenia and assessments were performed by administering the Positive and Negative Syndrome Scale (PANSS) for Schizophrenia (Kay et al., 1987). PANSS was scored by trained psychologists blind for TPH2 genotype at the start of treatment, and at weeks one and four. All patients were of German Caucasian origin and gave written informed consent to participate in the study. Both studies were approved by the appropriate ethics committees.

2.4. Genotyping and SNP Selection

We investigated 11 SNPs in total, six of which were selected because of their potential functional relevance (rs4570625, rs11178997, rs11178998, rs7954758, rs7305115, and, rs429027). Another 5 SNPs (table 2) were selected as supporting tagging SNPs based on HapMap LD information (The International HapMap Consortium, 2007). In all participants, DNA for the genotyping was isolated either from EDTA anticoagulated blood or permanent cell cultures received after transforming the lymphocytes with Epstein-Barr virus. The isolation followed the QIAGEN protocol for the Blood & Cell Culture DNA Maxi Kit (QIAGEN, Hilden, Germany). PCR was performed using 12.5 ng of DNA. We used SNP Genotyping Assays provided by Applied Biosystems. The procedure followed the protocol for Taqman® SNP-Genotyping also supplied by Applied Biosystems with the use of Taqman Universal PCR MasterMix (provided by Applied Biosystems, Foster City, CA, USA). Each of the assays consists of the unlabeled forward and reverse primers and two reporters, that are dye-labeled with FAM™ and VIC® and are designed for allelic discrimination of specific SNPs. Both alleles were scored in a single well by measuring the fluorescence at the end of the PCR using a Tecan Ultra 384 reader (Tecan, Crailsheim, Germany). Excitation- and emission-wavelengths for the Fam labeled probes were 485 and 535 nm and for the Vic labeled probes 535 and 590

nm, respectively. All SNPs had a call rate of at last 95%, in both case and control groups. After adjustment for multiple comparisons, there were no significant deviations from Hardy-Weinberg equilibrium (HWE) in any of the groups.

2.5. Data analysis

The case-control toolbox of FAMHAP (Herold & Becker, 2009) was used to perform statistical analysis of the case-control data. For each SNP, we used Armitage's trend test (ATT) (Armitage, 1955) to test for an association with schizophrenia. Maximum-likelihood haplotype frequencies were estimated with the Expectation-Maximization algorithm and significance of haplotype association was assessed with a likelihood ratio test. As suggested by Becker and Herold (2009), we systematically screened the whole gene and tested all 2-marker haplotypes for association. Adjustment for multiple testing was performed with Monte-Carlo simulations based on permutation of case-control status (Herold & Becker, 2009). The methods also account for the non-independence of the tests caused by linkage disequilibrium (LD) between SNPs (Herold & Becker, 2009).

The TPH2 haplotype yielding a significant association with schizophrenia was then tested for their effect on electrophysiological and cognitive endophenotypes as well as drug treatment response.

Cognitive data were analyzed by univariate ANOVA with TPH2 haplotype as independent variable and cognitive function as dependent variable. Within these analyses, age, gender, and pre-morbid verbal intelligence were controlled for. Analyses of covariance (ANCOVA) with sex, smoking, antipsychotic medication status, and age as covariates were used to analyze ASR parameters (Quednow et al., 2011; Quednow et al., 2008b; Quednow et al., 2010).

The time course of the treatment response, stratified by haplotype groups, was assessed by repeated-measurements ANCOVA (Admission, week 1, week 4) whereby the TPH2 haplotype served as factor and the respective PANSS value at admission served as covariate. To test for the distribution of gender regarding the genotype groups in both samples we made use of Pearson chi-square-test. Differences between the haplotype groups concerning the age of the patients and PANSS values at admission were assessed by variance analysis. The level of significance was set at 0.05 (two-tailed). Statistical analyses were performed using

SPSS statistical package 15.0 (SPSS Corp., Chicago, Illinois, USA). LD analysis was performed using Haploview (Barrett et al., 2005).

3. Results

3.1. Association of TPH2 with schizophrenia

Table 2 gives an overview over the eleven TPH2 SNP variants investigated. The association results for the discovery study can be found in table 3. In the discovery sample, rs10784941 showed strongest evidence for association (p=0.009, OR minor allele 0.82 [0.71-0.95]). The result remained significant after MC-simulation based adjustment for multiple SNPs tested (p=0.048; 1,000,000 permutations). Furthermore, rs4565946, a SNP in strong LD (r^2=0.86) with rs10784941 also showed evidence for association (p=0.011, OR T- allele 0.83 [0.71-0.96]). Fig 1 presents the LD plot created with Haploview. As shown the first eight TPH2 variants are within one block and variants 9,10 and 11 can be found in the second block. As suggested by us elsewhere (Becker & Herold, 2009), we compared case and control haplotype frequencies for all two-SNP haplotypes and also for haplotypes extending over a complete block. The most significant haplotype distribution was obtained for rs4570625 and rs4565946 (table 4). The G-C haplotype showed an odds ratio of 1.20 [1.02-1.40] and an uncorrected p-value of 0.0046. In addition to the G-C haplotype, the rare T-T haplotype (frequency in cases 1.8%, in controls 0.3%) showed an odds ratio of 6.25 [2.14-18.23] and an unadjusted p-value of $1.96*10^{-7}$.

Since the most promising association results were found in the first block of TPH2, we followed up the respective SNPs in an independent case-control sample. The respective association results can be found in table 5. None of the SNPs showed significant association with schizophrenia. In particular, neither association of rs10784941 (p=0.403, OR 1-allele 1.05 [0.94-1.17]) nor of rs4565946 (p=0.387, OR of T-allel 0.95 [0.85-1.06]) could be replicated. The common haplotype distribution of rs4570625 and rs4565946 in the replication sample can be found in table 6. The rare T-T haplotype was not present in the replication sample and, therefore, could not be investigated. When testing one sided the G-C haplotype showed a trend (p=0.054) that was consistent with the first study. The association failed to reach significance when tested two-sided (OR 1.10 [0.98-1.24]; p=0.108). Other combinations of SNPs did not show improved haplotype significance levels.

3.2. Cognitive functioning and sensorimotor gating in dependence from TPH2

For the analysis of cognitive, PPI, and pharmacogenetic data, we stratified the schizophrenia patients according to the TPH2 haplotype, which was found to be associated with schizophrenia in the first case control association analysis. Patients were classified in either having (one or two times) or not having this particular haplotype.

Cognitive functioning was not affected by the rs4570625-rs4565946 G-C haplotype in the schizophrenia patients (all $p>.05$). However, the rare T-T haplotype was significantly related with reduced processing speed as measured by the digit-symbol-substitution-task (DSST). Thus carriers of this haplotype only processed 39.1 items (SD=10.6) on average while non-carriers achieved an average score of 49.3 items (SD=10.5) ($F(1/188)=8.73$, $p=.004$) controlling for age, gender, and pre-morbid verbal intelligence (figure 2). After correction for multiple testing, no effect was found for any of the remaining cognitive functions.

Interestingly, in single ANCOVAs corrected for sex, smoking, antipsychotic medication status, and age, PPI was also significantly associated with the T-T haplotype and the G-T haplotype. Carriers of the T-T haplotype but also of the G-T haplotype displayed worse sensorimotor gating functions (table 7). After correction for multiple testing only the effect of the T-T haplotype remained significant. The startle amplitude and habituation was not associated with any of the investigated TPH2 SNPs.

3.3. Psychopathology during antipsychotic therapy in dependence from TPH2

The improvement of positive, negative, general psychopathology symptoms and the total PANSS score showed no significant effect, neither for the eleven TPH2 variants (data not presented here) nor for the TPH2 rs4570625-rs4565946 G-C and T-T haplotype. There were no differences regarding age, gender, positive, negative, general psychopathology and total PANSS values at admission between the eleven TPH2 variants and the G-C haplotype for the overall sample used for the pharmacogenetic analysis. The time course of the treatment response (admission-week1- week 4) in dependence from TPH2 G-C haplotype is shown in table 8.

4. Discussion

TPH2 has up to now been linked to psychiatric disorders like bipolar disorder (Lin et al., 2007), suicide (Zhou et al., 2005; Zill et al., 2004) and early onset obsessive compulsive disorder (Mössner et al., 2006b). Studies investigating the association of TPH2 variants with schizophrenia or the response to antipsychotic medication in dependence from TPH2 genotypes, have until now been rare. These results prompted us to investigate the association of TPH2 with schizophrenia and the influence of TPH2 variants on endophenotypes like cognition, prepulse inhibition and treatment response in schizophrenia.

Association analysis of variants of the TPH2 gene and schizophrenia in two independent case-control samples yielded inconclusive results. In our discovery sample, single-marker analysis was significant after adjustment for multiple testing. In addition to that, we observed strong association of rs4570625-rs4565946 haplotypes with schizophrenia. Both the G-C haplotype, which was previously implicated as leading to increased susceptibility for Tourette syndrome (Mössner et al., 2007), and the rare T-T haplotype showed evidence for increased risked of schizophrenia. However, these results could not be replicated in our second sample. The rare T-T haplotype was not present in the second study although it comprised more individuals. One might speculate that haplotype is in LD with a rare variant that exists only in the location the individuals of the first study were recruited from. On the other hand, it is also possible that a small number of genotyping errors at one of the SNPs have led to an artifact. Such errors are typically not detectable by the application of QC criteria that focus on single SNPs (Steffens et al., 2010).

Our replication sample was well-powered to detect an effect of the magnitude observed in the first study (rs10784941, OR 0.82[0.71-0.95]): computations with the Genetic Power Calculator (Purcell et al., 2003) yielded a power of 91.5% to replicate the finding. However, if one assumes an overestimation of the effect in the first study, and postulates an effect equal to the limit of the confidence interval (OR= 0.95), the power is only 17%. Indeed, the effect size of the G-allele in the replication sample is 0.95 (please note that the minor allele of both studies do not coincide, since allele frequencies are close to 0.5) which would be consistent with a very small effect. In line with this, the second most frequent G-C haplotype, showed a trend that was consistent with the initial study. However, since it failed to reach significance, further

studies are needed to enlighten the role of the TPH2 rs4570625-rs4565946 G-C haplotype

In a subsample with available cognitive endophenotypes we observed altered processing speed due to a TPH2 haplotype. Carriers of the schizophrenia associated rare rs4570625-rs4565946 T-T haplotype coded significantly less digit-symbol combinations compared to non-carriers. The level of performance reached at the digit-symbol-substitution-task (DSST) is a very promising endophenotype for schizophrenia. Patients score approximately one and a half standard deviation below healthy comparison subjects (Dickinson et al., 2007). A comparative twin study found adequate heritability of 68% of the DSST (Swan & Carmelli, 2002). TPH2, in particular the T-allele of the rs4570625, has been previously related to cognitive functions in healthy populations and ADHD patients as well (Baehne et al., 2009; Osinsky et al., 2009; Reuter et al., 2007; Strobel et al., 2007). Moreover, Reuter and colleagues (2008) showed significantly increased activation in carriers of the TT genotype of this variant in the frontal and motor cortex while performing a working memory task in the fMRI. This finding underlines the importance of TPH2 for complex cognitive functions of frontal and prefrontal cortical areas. In line with this DSST result, carriers of the T-T haplotype also displayed disrupted sensorimotor gating of the ASR, which is an established endophenotype of schizophrenia as well (Gottesman & Gould, 2003; Quednow et al., 2008a). We have previously shown that other variants from the serotonin system such as HT2A receptor SNPs affect sensorimotor gating likewise (Quednow et al., 2008b; Quednow et al., 2009). Thus, in future it would be of high interest to investigate gene-gene interactions of TPH2 and the HT2A receptor SNPs regarding sensorimotor gating but also with regard to the risk of schizophrenia. Interestingly, in single ANCOVAs corrected for sex, smoking, antipsychotic medication status, and age, PPI was also significantly associated with the T-T haplotype and the G-T haplotype, which is in line with the assumption that a PPI deficit represents an endophenotype of schizophrenia (Gottesman & Gould, 2003; Quednow et al., 2008a).

Pharmacogenetic analysis focussing on the eleven TPH2 variants and the relevant rs4570625-rs4565946 G-C haplotype in a smaller subsample of 210 patients did not show any association neither of the eleven variants (data not presented here) nor of the G-C and the T-T haplotype with response to antipsychotic medication after

four weeks of treatment administering the PANSS. We are not able to estimate the long-term effect of the interaction between TPH2 haplotype and treatment outcome because of the short period of assessment. However, it has been shown for other variants that the pharmacogenetic influence on outcome is similar at 4 weeks and 2–3 months (Mössner et al., 2009). Our findings did not confirm a major influence of TPH2 variants on treatment response to antipsychotics. Concerning the course of psychopathology in dependence from TPH2 Zhang et al. (2011) found an association of rs4570625 with the PANSS positive subscale. T/T carriers had higher positive symptom scores than G/G and G/T carriers (P=0.043 and 0.031, respectively). However, their results were not corrected for multiple testing and in contrast to the actual study their results were not based on repeated measurements. We could not find any association of the eleven TPH2 variants and TPH2 rs4570625-rs4565946 G-C and T-T haplotype on PANSS scores at baseline and in the course of antipsychotic treatment.

What are the limitations of our study? We have presented results from a two-stage association analysis of TPH2 in a Caucasian population. Despite considerable sample size, we were not able to significantly replicate interesting findings from our discovery study. Even larger sample size would be required to replicate our initial finding if that was driven by some winner's course. The common rs4570625-rs4565946 G-C haplotype showed a trend in the second sample, but failed to reach significance. The strongly associated, rare rs4570625-rs4565946 T-T haplotype was absent in our replication study, recruited from a geographic region about 400 km away from the recruiting region of the initial study, but was also related to a cognitive (processing speed) and a electrophysiological (sensorimotor gating) endophenotype of schizophrenia in subsamples of the first study, thus, giving some support for a true finding. On the other hand, these results have to be treated with some caution since the respective subsamples were rather small in comparison to the association samples. We also have to emphasize that most patients of the sub-samples were under antipsychotic treatment which is known to have a potential impact on cognition (Quednow et al, 2006; Tandon, 2011). However, since all patients were under stable medication at the point of the analysis and since we adjusted for medication status in the statistical analysis, we believe that this potential influence on the results could be minimized. Finally, association with response to psychotic treatment could not be observed for any of the investigated SNPs or haplotypes.

In summary, the question of the relevance of TPH2 genetic variation for schizophrenia or schizophrenia endophenotypes could not be answered finally. Our findings reveal only a minor role of TPH2 haplotypes for schizophrenia.

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Conflict of interest:

None declared.

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Figure legend:

Fig. 1: LD plot of the investigated TPH2 variants created with Haploview.

Figure 2: Performance of schizophrenia patients carrying the rare TPH2 rs4570625-rs4565946 T-T haplotype in the digit-symbol-substitution-task. Carriers of this haplotype only processed 39.1 items (SD = 10.6) on average while non-carriers achieved an average score of 49.3 items (SD = 10.5) ($F = 8.73$, $df = 1/188$, $p = .004$).

Table(s)

Table 1: Description of TPH2 variants, amino acid change and localization on gene

rs number	Nucleotide exchange	Location in Gene	Location on Chromosome
rs4570625	T -703 G	Promoter	chr12:72331923
rs11178997	T -473 A	Promoter	chr12:72332153
rs11178998	A 90 G	5´UTR (Exon1)	chr12:72332715
rs4341581	intronic (G/T)	Intron 1	chr12:72335073
rs7954758	intronic (A/G)	Intron 2	chr12:72335794
rs10784941	intronic (A/G)	Intron 2	chr12:72336512
rs4565946	intronic (C/T)	Intron 2	chr12:72336769
rs11179000	intronic (A/T)	Intron 4	chr12:72338628
rs7305115	G 40237 A (Pro312Pro)	Exon 7	chr12:72372862
rs4290270	A 83610 T (Ala375Ala)	Exon 9	chr12:72416235
rs17110747	G 93329 A	3´UTR (Exon11)	chr12:72425954

Note: the amino acid is also indicated, where applicable

Table(s)

Table 2: Association of TPH2 variants with schizophrenia in the discovery sample

rs number	Minor/major allele	Minor allele frequencies		*p* value ATT[1]	OR[2] and confidence interval
		cases	controls		
rs4570625	T/G	0.22	0.20	0.2340	1.12 [0.30-1.34]
rs11178997	A/T	0.07	0.06	0.3490	1.16 [0.85-1.57]
rs11178998	G/A	0.06	0.06	0.4360	1.13 [0.83-1.54]
rs4341581	G/T	0.04	0.04	0.8870	1.03 [0.71-1.49]
rs7954758	G/A	0.07	0.06	0.3430	1.16 [0.85-1.57]
rs10784941	G/A	0.47	0.52	**0.0091**	0.82 [0.71-0.95]
rs4565946	T/C	0.43	0.48	**0.0106**	0.83 [0.71-0.96]
rs11179000	T/A	0.24	0.21	0.0668	1.18 [0.99-1.40]
rs7305115	A/G	0.41	0.39	0.2040	1.10 [0.95-1.28]
rs4290270	A/T	0.36	0.35	0.5320	1.05 [0.90-1.22]
rs17110747	A/G	0.15	0.13	0.1800	1.16 [0.94-1.43]

[1] Armitage trend test

[2] Odds ratios are given for minor allele

Table(s)

Table 3: Haplotype frequencies and accociation results for haplotype rs4570625-rs4565946 in the discovery sample

Haplotype	Frequencies		Odds ratio and confidence interval	*p* value
	Cases	Controls		
G C	0.364	0.323	1.20 [1.02-1.40]	0.0046100
G T	0.418	0.481	0.78 [0.67-0.90]	0.0002490
T C	0.200	0.194	1.04 [0.87-1.26]	n.s.[1]
T T	0.018	0.003	6.25 [2.14-18.23]	0.0000002

[1]not significant: *p*-value > 0.2

Table(s)

Table 4: Association of TPH2 variants with schizophrenia in the replication sample

rs number	Minor/major allele	Minor allele frequencies		*p* value ATT[1]	OR[2] and confidence interval
		cases	controls		
rs4570625	T/G	0.20	0.21	0.3710	0.94 [0.82-1.08]
rs11178997	A/T	0.06	0.07	0.2190	0.87 [0.69-1.09]
rs11178998	G/A	0.06	0.07	0.1400	0.84 [0.67-1.06]
rs4341581	G/T	0.04	0.04	0.9920	1.00 [0-75-1.32]
rs7954758	G/A	0.06	0.07	0.2710	0.88 [0.70-1.10]
rs10784941	A/G	0.48	0.49	0.4030	1.05 [0.94-1.17]
rs4565946	T/C	0.45	0.46	0.3870	0.95 [0.85-1.06]

[1] Armitage trend test

[2] Odds ratios are given for minor allele

Table(s)

Table 5: Haplotype frequencies and accociation results for haplotype rs4570625-rs4565946 in thereplication sample

Haplotype	Frequencies		Odds ratio and confidence interval	*p* value
	Cases	Controls		
G C	0.352	0.330	1.10 [0.98-1.24]	0.054
G T	0.445	0.457	0.95 [0.85-1.06]	n.s.[1]
T C	0.204	0.212	0.95 [0.83-1.09]	n.s.[1]
T T	0.000	0.000	-	-

[1]not significant: p-value > 0.2

Table(s)

Table 6: Prepulse-Inhibition (PPI) values (means and standard errors of means in parentheses) for haplotype rs4570625-rs4565946 in 68 schizophrenia patients

Haplotype	PPI		*p* value 1
	Haplotype	Other	
G C (n=53)	44.5 (4.1)	28.0 (8.8)	0.097
G T (n=41)	34.8 (4.5)	52.8 (5.9)	**0.020**
T C (n=27)	34.2 (5.8)	46.6 (4.9)	0.113
T T (n=14)	22.3 (7.7)	47.1 (3.9)	**0.006**

[1] ANCOVA corrected for age, sex, smoking and antipsychotic medication

Table(s)

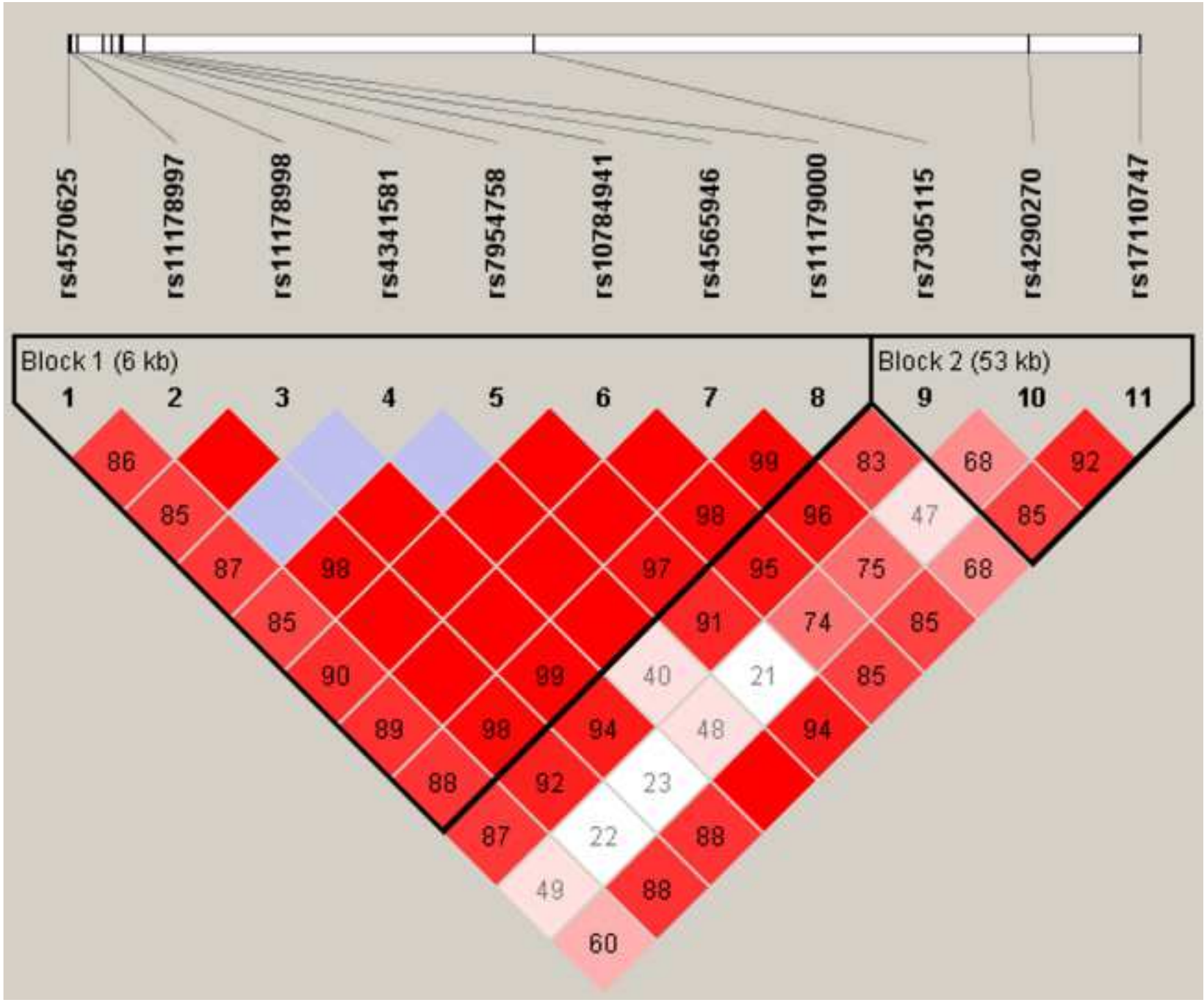
Table 7: Time course of treatment response on PANSS scales in 210 patients stratified by TPH2 haplotype rs4570625-rs4565946

Positive and negative syndrome scale for Schizophrenia: PANSS	TPH2 Haplotype GC	Symptoms at admission	Symptoms at week 1	Symptoms at week 4	*p* Value[1]
Positive symptoms	0x (n=83)	22.70 +- 6.69	16.40 +- 4.36	13.57 +-3.93	0.74
	1x (n=100)	22.14 +- 4.72	16.54 +- 4.64	13.42 +- 3.95	
	2x (n=27)	21.30 +- 4.22	16.04 +- 4.86	13.04 +- 3.09	
Negative symptoms	0x (n=83)	21.17 +- 5.13	18.59 +- 5.46	16.63 +- 3.78	0.71
	1x (n=100)	20.87 +- 6.23	18.90 +- 6.36	16.52 +- 5.46	
	2x (n=27)	21.63 +- 5.69	19.22 +- 6.00	18.15 +- 4.61	
General psychopathology	0x (n=83)	42.76 +- 10.20	36.28 +- 8.55	32.63 +- 7.12	0.26
	1x (n=100)	42.42 +- 9.80	36.32 +- 9.18	30.88 +- 7.82	
	2x (n=27)	42.00 +- 8.21	37.37 +- 10.14	32.96 +- 7.94	
Total PANSS score	0x (n=83)	86.69 +- 18.39	71.10 +- 16.79	62.96 +- 13.43	0.41
	1x (n=100)	85.63 +- 18.31	71.81 +- 17.97	61.00 +- 15.60	
	2x (n=27)	84.70 +- 16.52	72.67 +- 19. 46	64.00 +- 13.66	

Symptoms are reported as mean and standard deviation

[1] *p* value for repeated measurements analysis of variance (admission, week 1, week 4), independent variable: TPH2 haplotype (stratified according to no haplotype or one or two times haplotype), covariate: respective PANSS value at admission

Figure(s)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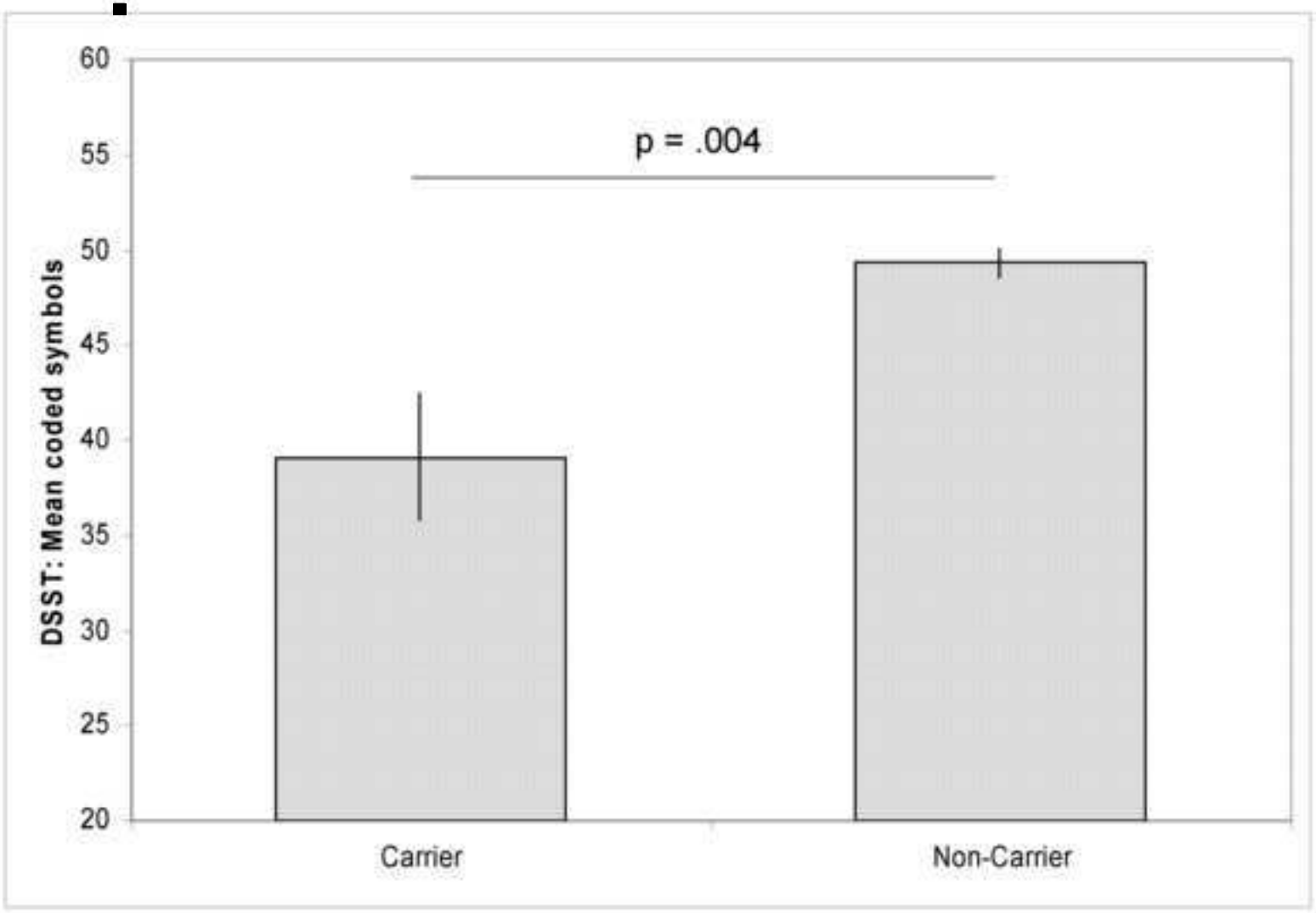
Figure(s)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